

additional fees which may be required, or credit any overpayment, to Deposit Account No. 01-2507.

In the Claims

1. (twice amended) A recombinant Ca^{2+} dependent monoclonal antibody or antibody fragment comprising the hypervariable region of the monoclonal antibody produced by the hybridoma deposited with the American Type Culture Collection as ATCC No. HB 9892 immunoreactive with a first epitope in the activation peptide region of the heavy chain of Protein C defined by E D Q V D P R L I D G K (Sequence ID No. 1) in combination with a second epitope consisting of calcium ions, where the antibody inhibits Protein C activation by thrombin-thrombomodulin[, and wherein the antibody is encoded in part by a nucleotide sequence selected from the group consisting of ATGGGCAGGC TTTCTTCTTC ATTCTTGCTA CTGATTGCCC CTGCATATGT CCTGTCCCAG GTTACTCTGA AAGAGTCTGG CCCTGGGATA TTGCAGCCCT CCCAGACCCT CACTCTGACT TGTCTCTCT CTGGGTTTTC ACTGAGGACT TCTGGTATGG GTGTAGGCTG GATTCGTCAG CCTTCAGGGA AGGGTCTGGA GTGGCTGGCA CACATTGTTGTT GGGATGATGA CAAGCGCTAT AACCCAGTCC TGAAGAGCCG ACTGATAATC TCCAAGGATA CCTCCAGGAA ACAGGTATTC CTCAAGATCG CCAGTGTGGA CACTGCAGAT ACTGCCACAT ACTACTGTGT TCGAATGATG GATGATTACG ACGCTATGGA CTACTGGGGT CAAGGAACCT CAGTCACCGT CTCCTCT (Sequence ID No. 9); CAG GTTACTCTGA AAGAGTCTGG CCCTGGGATA TTGCAGCCCT

U.S.S.N. 08/259,321

Filed: June 10, 1994

AMENDMENT UNDER 37 C.F.R. §1.129a

CCCAGACCCT CACTCTGACT TGTTCTCTCT CTGGGTTTTC ACTGAGGACT
TCTGGTATGG GTGTAGGCTG GATTCGTCAG CCTTCAGGGA AGGGTCTGGA
GTGGCTGGCA CACATTTGGT GGGATGATGA CAAGCGCTAT AACCCAGTCC
TGAAGAGCCG ACTGATAATC TCCAAGGATA CCTCCAGGAA ACAGGTATTC
CTCAAGATCG CCAGTGTGGA CACTGCAGAT ACTGCCACAT ACTACTGTGT
TCGAATGATG GATGATTACG ACGCTATGGA CTACTGGGGT CAAGGAACCT
CAGTCACCGT CTCCTCT (nucleotides 58 to 417 of Sequence ID No. 9); ATGGATTTTC
AGGTGCAGAT TTTCAGCTTC CTGCTAATCA GTGCCTCAGT CATAATGTCC
AGAGGACAAA TTATTCTCAC CCAGTCTCCG GCAATCATGT CTGCATCTCT
GGGGGAGGAG ATCACCCTAA CCTGCAGTGC CACTTCGAGT GTAACCTACG
TCCACTGGTA CCAGCAGAAG TCAGGCACTT CTCCCAAACCT CTTGATTTAT
GGGACATCCA ACCTGGCTTC TGGAGTCCCT TCTCGTTTCA GTGGCAGTGG
GTCTGGGACC TTTTATTCTC TCACAGTCAG CAGTGTGGAG GCTGAAGATG
CTGCCGATTA TTAAGTCCAT CAGTGGGAATA GTTATCCGCA CACGTTCCGA
GGGGGGACCA AGCTGGAAAT AAAACGG (Sequence ID No. 11); CAAA
TTATTCTCAC CCAGTCTCCG GCAATCATGT CTGCATCTCT GGGGGAGGAG
ATCACCCTAA CCTGCAGTGC CACTTCGAGT GTAACCTACG TCCACTGGTA
CCAGCAGAAG TCAGGCACTT CTCCCAAACCT CTTGATTTAT GGGACATCCA
ACCTGGCTTC TGGAGTCCCT TCTCGTTTCA GTGGCAGTGG GTCTGGGACC
TTTTATTCTC TCACAGTCAG CAGTGTGGAG GCTGAAGATG CTGCCGATTA

sub C1
B1
cont
TTACTGCCAT CAGTGGGAATA GTTATCCGCA CACGTTCCGGA GGGGGGACCA

AGCTGGAAAT AAAACGG (nucleotides 67 to 387 of Sequence ID No. 11); and degenerate

sequences thereof, and wherein the antibody is not the HPC-4 antibody deposited with the

American Type Culture Collection as ATCC No. HB 9892], wherein the antibody is

expressed in bacterial cells or contains human amino acid sequence.

sub D2
B2
3. (twice amended) The antibody of claim 1 [containing] comprising human amino

acid sequence [other than the sequence defining the epitope binding specificity] in the

constant domain or framework regions of the variable domain.

14. (twice amended) A method of making a recombinant Ca^{2+} dependent

monoclonal antibody immunoreactive with a first epitope in the activation peptide region of

sub C3
B3
the heavy chain of Protein C defined by E D Q V D R R L I D G K (Sequence ID No. 1) in

combination with a second epitope consisting of calcium ions, where the antibody inhibits

Protein C activation by thrombin-thrombomodulin, by expressing nucleotide sequence

encoding the [antibody, wherein the antibody is encoded in part by a nucleotide sequence

selected from the group consisting of ATGGGCAGGC TTTCTTCTTC ATTCTTGCTA

CTGATTGCCC CTGCATATGT CCTGTCCCAG GTTACTCTGA AAGAGTCTGG

CCCTGGGATA TTGCAGCCCT CCCAGACCCT CACTCTGACT TGTTCTCTCT

CTGGGTTTTTCT ACTGAGGACT TCTGGTATGG GTGTAGGCTG GATTCGTCAG

CCTTCAGGGA AGGGTCTGGA GTGGCTGGCA CACATTTGGT GGGATGATGA

CAAGCGCTAT AACCCAGTCC TGAAGAGCCG ACTGATAATC TCCAAGGATA

U.S.S.N. 08/259,321

Filed: June 10, 1994

AMENDMENT UNDER 37 C.F.R. §1.129a

*Sub
8C3
B
Cont.*

CCTCCAGGAA ACAGGTATTC CTCAAGATCG CCAGTGTGGA CACTGCAGAT
ACTGCCACAT ACTACTGTGT TCGAATGATG GATGATTACG ACGCTATGGA
CTACTGGGGT CAAGGAACCT CAGTCACCGT CTCCTCT (Sequence ID No. 9); CAG
GTTACTCTGA AAGAGTCTGG CCCTGGGATA TTGCAGCCCT CCCAGACCCCT
CACTCTGACT TGTCTCTCT CTGGGTTTTC ACTGAGGACT TCTGGTATGG
GTGTAGGCTG GATTCGTCAG CCTTCAGGGA AGGGTCTGGA GTGGCTGGCA
CACATTTGGT GGGATGATGA CAAGCGCTAT AACCCAGTCC TGAAGAGCCG
ACTGATAATC TCCAAGGATA CCTCCAGGAA ACAGGTATTC CTCAAGATCG
CCAGTGTGGA CACTGCAGAT ACTGCCACAT ACTACTGTGT TCGAATGATG
GATGATTACG ACGCTATGGA CTACTGGGGT CAAGGAACCT CAGTCACCGT
CTCCTCT (nucleotides 58 to 417 of Sequence ID No. 9); ATGGATTTTC AGGTGCAGAT
TTTCAGCTTC CTGCTAATCA GTGCCTCAGT CATAATGTCC AGAGGACAAA
TTATTCTCAC CCAGTCTCCG GCAATCATGT CTGCATCTCT GGGGGAGGAG
ATCACCCTAA CCTGCAGTGC CACTTCGAGT GTAACCTACG TCCACTGGTA
CCAGCAGAAG TCAGGCACTT CTCCCAAACCT CTTGATTTAT GGGACATCCA
ACCTGGCTTC TGGAGTCCCT TCTCGTTTCA GTGGCAGTGG GTCTGGGACC
TTTTATTCTC TCACAGTCAG CAGTGTGGAG GCTGAAGATG CTGCCGATTA
TTACTGCCAT CAGTGGAATA GTTATCCGCA CACGTTCCGA GGGGGGACCA
AGCTGGAAAT AAAACGG (Sequence ID No. 11); CAAA TTATTCTCAC
CCAGTCTCCG GCAATCATGT CTGCATCTCT GGGGGAGGAG ATCACCCTAA

Sub
C3
B
cont

CCTGCAGTGC CACTTCGAGT GTAACCTACG TCCACTGGTA CCAGCAGAAG
TCAGGCACTT CTCCCAAACCT CTTGATTAT GGGACATCCA ACCTGGCTTC
TGGAGTCCCT TCTCGTTTCA GTGGCAGTGG GTCTGGGACC TTTTATTCTC
TCACAGTCAG CAGTGTGGAG GCTGAAGATG CTGCCGATTA TTA CTGCCAT
CAGTGAATA GTTATCCGCA CACGTTCGGA GGGGGGACCA AGCTGGAAAT
AAAACGG (nucleotides 67 to 387 of Sequence ID No. 11); and degenerate sequences
thereof, and is not 1 HPC-4] hypervariable region of the monoclonal antibody expressed by
the hybridoma [as] deposited with the American Type Culture Collection as ATCC No. HB
9892 in bacteria.

Sub
C4
B4

17. (twice amended) The method of claim 14 further comprising inserting human
sequence into the antibody in [place of animal sequence other than the sequence defining the
epitope binding specificity] the constant domain or framework regions of the variable
domain.

20. (amended) [A] The recombinant [HPC-4] antibody [as deposited with the
American Type Culture Collection as ATCC No. 9892 expressed as a fusion protein] of
claim 1 having coupled thereto a peptide sequence.

5
B

21. (amended) [A] The method [for making a recombinant HPC-4 antibody
wherein a nucleotide sequence encoding HPC-4 antibody as deposited with the American
Type Culture Collection as ATCC No. 9892] of claim 14 wherein the nucleotide sequence
encoding the recombinant antibody is ligated to a sequence encoding a [different protein]